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Ubiquitin-dependent regulation of immune and inflammatory signaling pathways

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Modification of proteins with ubiquitin is a key mechanism for the regulation of a wide range of cellular functions. The outcome of the modification is determined by the way ubiquitin molecules are linked to each other. Linear (M1-linked) ubiquitin chains play an important role in the regulation of immune and inflammatory signaling pathways and contribute to the activation of NF- κ B. They are synthesized by the E3 ubiquitin ligase LUBAC (linear ubiquitin chain assembly complex) that is composed of at least three subunits named HOIL-1L, HOIP and SHARPIN. LUBAC belongs to the RBR (RING-inbetween-RING) family of E3 ligases that combine the properties of RING and HECT ligases and act as RING/HECT hybrids. Indeed, we have recently shown that linear ubiquitin chain synthesis proceeds via ubiquitin thioester intermediate formed by the HOIP subunit before subsequent transfer onto the target. I will present a combination of structural and biochemical data that provide a molecular explanation how this unusual E3 ligase complex promotes the synthesis of linear ubiquitin chains with high specificity, regardless of the E2 conjugating enzyme it works with.

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